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ICAM-1 costimulation induces IL-2 but inhibits IL-10 production in superantigen-activated human CD4+ T cells.

Labuda T, Wendt J, Hedlund G, Dohlsten M.

Department of Tumor Immunology, University of Lund, Lund, Sweden.

We have previously reported that costimulatory pathways including B7-CD28 and lymphocyte function-associated antigen-3 (LFA-3)-CD2 shape distinct activation profiles in human CD4+ T cells. We now show that superantigen (SAg), in combination with intracellular adhesion molecule-1 (ICAM-1) costimulation drives a proliferative response accompanied by high levels of interleukin-2 (IL-2) and moderate levels of interferon-gamma (IFN-gamma) and tumour necrosis factor (TNF). This response profile differs from that observed in B7 or LFA-3 costimulated T cells because our previous results showed that B7-CD28 costimulation was accompanied by high levels of IL-2, IFN-gamma and TNF, whereas LFA-3 was a potent inducer of IFN-gamma and TNF, but had little influence on IL-2 production. The ICAM-1-induced IL-2 production could efficiently be abrogated with monoclonal antibody (mAb) against ICAM-1 or LFA-1, showing that the activation is dependent of a functional ICAM-1-LFA-1 pathway. SAg-induced IL-2, IFN-gamma and TNF were detected in both CD4+ and CD8+ T cells, whereas production of IL-10 was restricted to CD4+ T cells. A major finding in the present study was that ICAM-1 costimulation strongly inhibits IL-10 production in CD4+ T cells. Our data demonstrate that ICAM-1 costimulation is sufficient to induce large amounts of IL-2. The presence of ICAM-1 results in suppression of IL-10 production in T helper (Th) cells, which may favour the development of Th1 and not Th2 T cells.

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Dendritic antigen-presenting cells from the peripheral blood of renal-cell-carcinoma patients.

Radmayr C, Bock G, Hobisch A, Klocker H, Bartsch G, Thurnher M.

Department of Urology, University of Innsbruck, Austria.

Dendritic cells are considered to be the initiators of immune responses, including those directed against tumors. Clinical research on dendritic cells was long hampered by the limited availability of these cells. The recent identification of cytokine combinations that mobilize dendritic cells with potent antigen-presenting cell function from peripheral blood represented a major progress. We show in this study that substantial numbers of dendritic cells can be obtained from the peripheral blood of patients with renal-cell carcinoma. The procedure requires a relatively small blood sample (40 ml) and avoids both priming of the patient with granulocyte-colony stimulating factor and leukapheresis. Approximately 2 to 8 million cells with the characteristics of dendritic cells could be obtained: phase-contrast microscopy revealed the typical cytoplasmic processes or veils; phenotypic analysis confirmed expression of dendritic-cell-associated molecules, including MHC class II, CD1a, CD4, ICAM-1 (CD54), LFA-3 (CD58), B7-1 (CD80) and B7-2 (CD86), and absence of T-cell, B-cell and monocyte markers; in addition, these cells rapidly attached to and migrated on collagen-type-1-coated surfaces. Interestingly, attachment was accompanied by acquisition of the CD14 antigen; functionally, cultured dendritic cells proved to be very potent co-stimulators of the phytohemagglutinin-induced proliferation of autologous tumor-infiltrating lymphocytes. The reproducible growth of functional dendritic cells from cancer patients is encouraging for the design of immunotherapy protocols.

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The primary alloresponse of human CD4+ T cells is dependent on B7 (CD80), augmented by CD58, but relatively uninfluenced by CD54 expression.

Hargreaves R, Logiou V, Lechler R.

Department of Immunology, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK.

Conflicting data have been reported regarding the relative abilities of B7, ICAM-1 and LFA-3 to provide co-stimulation for the induction of a primary T cell alloproliferative response. A series of naturally HLA-DR-expressing cell lines and panels of human and murine transfectants expressing DR alloantigens in conjunction with combinations of mouse or human B7.1, human LFA-3 and human ICAM-1 were used to analyse the contributions of these molecules to primary alloproliferative responses by adult and cord blood CD4+ T cells. The results demonstrated that B7 expression is required, and may be sufficient for the induction of a primary alloresponse. The allostimulation observed in response to DR-expressing murine DAP.3 cells, that constitutively express B7.1, was inhibited by the presence of the murine cytolytic T lymphocyte-associated antigen 4-human Fc gamma 11 fusion protein, suggesting that mouse B7.1 provides sufficient costimulation for a primary human alloproliferative response. Expression of supranormal levels of human B7.1 on the allostimulator cells led to a reduction in the proliferative response, suggesting that an optimal level of B7 exists which, if exceeded, leads to inhibition. Co-expression of LFA-3 with B7.1 by the allostimulator cells caused a marked increase in the proliferative response. Expression of ICAM-1a had relatively little effect. No differences were seen in the co-stimulatory requirements of naive cord blood versus CD45RO adult T cells. There results highlight the key molecular interactions that govern immunogenicity with relevance to inhibiting unwanted immune response to transplanted tissues and provoking anti-tumour immunity.

PMID: 7495758 [PubMed - indexed for MEDLINE]

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The antigen-presenting cell function of Reed-Sternberg cells.

Delabie J, Chan WC, Weisenburger DD, De Wolf-Peeters C.

Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha 68198-3115, USA.

Reed-Sternberg cells, the neoplastic cells of Hodgkin's disease, express all membrane molecules required to function as antigen-presenting cells (APCs), such as major histocompatibility complex (MHC) class II antigens and the recently characterized B7 proteins, which are of critical importance for APC to adequately stimulate CD4+ T cells. As APC do, Reed-Sternberg cells also express the adhesion molecules ICAM-1 (CD54) and LFA-3 (CD58), via which T cells are able to adhere to the cell. MHC antigens, B7 proteins as well as the adhesion molecules are expressed by Reed-Sternberg cells in virtually all cases of Hodgkin's disease, irrespective of the subtype. In vitro studies have shown that Hodgkin's disease-derived cell lines are potent stimulators of mixed lymphocyte cultures and that the MHC antigens, B7 proteins and the adhesion molecules, expressed by Hodgkin's disease-derived cell lines, are essential for such a function. Taken together, these data strongly suggest that Reed-Sternberg cells function as APC in vivo, and that the APC function of the cell is a major common denominator of Hodgkin's disease. The APC function of Reed-Sternberg cells does not support the hypothesis that they derive from dendritic cells, since activated B and T cells may also exert an APC function. Analysis of the antigens that are potentially expressed by Reed-Sternberg cells may greatly advance our knowledge on the pathogenesis of Hodgkin's disease and may allow the development of immunotherapy as an alternative treatment method.

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Functional expression of adhesion receptors and costimulatory molecules by fresh and immortalized B-cell non-Hodgkin's lymphoma cells.

Vyth-Dreese FA, Dellemijn TA, van Oostveen JW, Feltkamp CA, Hekman A.

Division of Immunology, The Netherlands Cancer Institute, Amsterdam.

Peripheral blood lymphocytes of a patient with follicular B-cell non-Hodgkin's lymphoma (B-NHL) were immortalized in vitro by Epstein-Barr virus (EBV). Eight cell lines were obtained (termed BNS1, BNS2-1 through BNS2-7), which showed a pattern of idiotypic (id) Ig surface expression and Ig JH and kappa gene rearrangement, identical to that of the parent cells (termed NS), confirming their neoplastic origin. Induction of allogeneic T-cell proliferation by NS cells was mediated by HLA-DR, leukocyte function-associated antigen-1 (LFA-1), LFA-3, B7-1/CD80, and CTLA4 and resulted in the upregulation (LFA-3, intercellular adhesion molecule-1 [ICAM-1], CD40) and induction (B7-1/CD80, B7-2/CD86, L16/activated LFA-1) of accessory molecules on NS cells. In turn, responder T lymphocytes were induced to express B7-1/CD80, B7-2/CD86, CD40 ligand (CD40L), ICAM-1, L16/activated LFA-1, and HLA-DR, reflecting bidirectional signaling between T lymphocytes and B-NHL cells. Preactivation of NS cells by EBV transformation or CD40 engagement resulted in enhanced expression of accessory molecules and abolished the requirement for accessory cells during allostimulation. These resting and activated clonal B cells will be useful in further dissecting the requirements for B-NHL costimulation.

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Functional intercellular adhesion molecule-3 is expressed by freshly isolated epidermal Langerhans cells and is not regulated during culture.

Zambruno G, Cossarizza A, Zacchi V, Ottani D, Luppi AM, Giannetti A, Girolomoni G.

Istituto Dermopatico dell'Immacolate, IRCCS, Rome, Italy.

Activation of T lymphocytes by antigen-presenting cells requires the interaction of major histocompatibility complex/antigen complexes with the T-cell receptor as well as the binding of co-stimulatory molecules to receptors on T cells. Freshly isolated epidermal Langerhans cells (LC) do not display a significant number of co-stimulatory molecules. After short-term culture, LC express and then upregulate intercellular adhesion molecule-1 (ICAM-1) (CD54), leukocyte function-associated antigen (LFA)-3 (CD58), and B7-1 (CD80) accessory molecules and exhibit an enhanced antigen-presenting function. The present study examined the presence on human LC of the LFA-1 ligands ICAM-2 (CD102) and ICAM-3 (CD50) and their functional role in the activation of allogeneic T cells. Immunohistochemistry of skin sections and flow-cytometry analysis of freshly procured epidermal cell suspensions showed that LC (CD1a+ or HLA-DR+) expressed ICAM-3 but not ICAM-2. After 48-72-h culture in the presence of granulocyte/macrophage colony-stimulating factor, LC did not stain for ICAM-2 but expressed ICAM-3 at the same level as fresh cells. Incubation of both freshly isolated and cultured LC with monoclonal antibodies directed against ICAM-3 reduced T-cell proliferation (25-75% inhibition) in the primary allogeneic mixed leukocyte reaction assay; incubation of cultured LC with anti-ICAM-1 and anti-ICAM-3 synergistically reduced T-cell response. The results indicate that ICAM-3 is constitutively expressed and represents an important costimulatory molecule on freshly isolated LC but, in contrast to other accessory molecules, is not subjected to regulation during LC culture.

PMID: 7636303 [PubMed - indexed for MEDLINE]

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In situ behavior of human Langerhans cells in skin organ culture.

Rambukkana A, Bos JD, Irik D, Menko WJ, Kapsenberg ML, Das PK.

Department of Dermatology, University of Amsterdam, The Netherlands.

BACKGROUND: Epidermal Langerhans cells (ELC) play a critical role in the initiation of cutaneous immune responses. ELC are characterized by the expression of major histocompatibility complex (MHC) class II Ag and a number of adhesion/costimulatory molecules. Evidence suggests that cytokines induced within the epidermis regulate the functions of ELC, including their phenotypic expression. In the human system, no information is available regarding the behavior of the ELC in situ: their changes in morphology, expression of functional molecules or migration within the microenvironment. In the present study, using an ex vivo human skin organ culture model, we addressed the above questions and also examined the phenotypic modulation of ELC in situ by cytokines. EXPERIMENTAL DESIGN: Skin explants were cultured either in a Trowell-type method or free in the medium. Skin explants were cultured with and without cytokines and were processed for light and electron microscopy and for immunohistochemical definition of ELC phenotypes. RESULTS: In the Trowell-type skin organ culture, morphologic integrity of ELC, CD1a molecule, and Birbeck granules could be preserved intact up to 3 to 4 days in culture. During the first 3 days of culture, the intensity of MHC-II (HLA-DR, DP, and DQ) and CD1a expression on ELC increased sharply, and the dendritic appearance of ELC became more prominent at Day 3. Adhesion molecules, ICAM-1, LFA-3, HECA-452, sLx, and B7/BB1 were also spontaneously acquired in varying amounts by CD1a+ ELC after 3 days in culture. Significant increase of CD1a and ICAM-1 expression on ELC was observed within 12 hours, when skin explants were cultured free in the medium with GM-CSF and TNF-alpha, respectively. Further, we demonstrated spontaneous migration of ELC within the epidermis and then to the dermis during the Trowell-type skin culture. We also showed the migration of ELC out of the human skin when skin explants were cultured directly in the medium. CONCLUSIONS: Human ELC showed significant phenotypic changes within the epidermis and acquired migratory capacity during the skin organ culture. ELC in skin organ culture appear to undergo a phenotypic maturation within the epidermis. ELC in situ rapidly respond to GM-CSF and TNF-alpha by increasing the expression of CD1a and ICAM-1 molecules, respectively. These results suggest the modulation of phenotypic characteristics of ELC and their migration in response to the changes of

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Comparative accessory cell function of human peripheral blood dendritic cells and monocytes.

Thomas R, Davis LS, Lipsky PE.

Harold C. Simmons Arthritis Research Center, Dallas, TX.

The capacity of human peripheral blood (PB) dendritic cells (DC) and monocytes to facilitate T cell activation and the interaction molecules employed were compared. We have shown that precursors of DC constitute 2 to 3% of circulating PBMC, and can be isolated as CD33+CD14dim cells, whereas monocytes are CD33+CD14bright. Freshly obtained DC expressed similar densities of HLA-DR and the accessory molecules LFA-3, ICAM-1, and B7 as monocytes; after a 36-h incubation the expression of HLA-DR, ICAM-1, and B7 increased on both APC. Accessory cell function was examined in PB T cell cultures stimulated by suboptimal concentrations of immobilized mAb to CD3, and by stimulation of an allospecific T cell line. Freshly isolated monocytes and DC were comparable accessory cells in these assays, but their accessory function was increased by in vitro preincubation, although cultured DC and monocytes were comparably active. In contrast, DC were much more effective stimulators of freshly isolated allogeneic T cells than monocytes. DC were much more effective stimulators of freshly isolated allogeneic PB CD4+ naive and memory T cells than monocytes, whereas DC and monocytes were comparable accessory cells for memory and naive T cells stimulated with immobilized anti-CD3. The accessory molecules ICAM-1, LFA-3, and B7 were used comparably by DC and monocytes for accessory function in the presence of immobilized anti-CD3 and in the MLR, and none was unique for either APC population. These accessory molecules costimulated T cells in an additive fashion. Although immature blood DC and monocytes expressed minimal B7 and did not utilize it as an accessory molecule, B7 played an important role in the increased accessory function of differentiated APC. The results indicate that PB DC and monocytes function most efficiently after differentiation into mature cells that express increased amounts of MHC and other accessory molecules. Because DC and monocytes exhibit comparable accessory function in anti-CD3 T cell stimulation, differences in the expression of MHC molecules and/or their bound peptides are likely to explain the markedly enhanced capacity of DC to stimulate allogeneic PB T cells.

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Antigen-presenting human T cells and antigen-presenting B cells induce a similar cytokine profile in specific T cell clones.

Wyss-Coray T, Gallati H, Pracht I, Limat A, Mauri D, Frutig K, Pichler WJ.

Institute of Clinical Immunology, Inselspital, Bern, Switzerland.

One of the factors that may influence the cytokine secretion profile of a T cell is the antigen-presenting cell (APC). Since activated human T cells have been described to express major histocompatibility complex (MHC) class II molecules as well as costimulatory molecules for T cell activation, like e.g. ICAM-1, LFA-3 and B7, they might play a role as APC and be involved in the regulation of T-Tcell interactions. To define further the role of T cells as APC we tested their capacity to induce proliferation and cytokine production in peptide- or allospecific T cell clones and compared it with conventional APC, like B lymphoblasts (B-LCL) or HTLV-1-transformed T cells, or with non-classical APC, like activated keratinocytes or eosinophils. CD4+, DP-restricted T cell clones specific for a tetanus toxin peptide (amino acids 947-967) and CD4+, DR-restricted allospecific T cell clones produced interleukin (IL)-2, IL-4, tumor necrosis factor-alpha and interferon-gamma (IFN-gamma) after phorbol 12-myristate 13-acetate and ionomycin stimulation and a more restricted cytokine pattern after antigen stimulation. Dose-response curves revealed that the antigen-presenting capacity of activated, MHC class II+, B7+ T cells was comparable to the one of B-LCL. Both APC induced the same cytokine profile in the T cell clones despite a weaker proliferative response with T cells as APC. Suboptimal stimulations resulted in a lower IFN-gamma/IL-4 ratio. Cytokine-treated, MHC class II+ keratinocytes and eosinophils differed in the expression of adhesion molecules and their capacity to restimulate T cell clones. The strongly ICAM-1-positive keratinocytes induced rather high cytokine levels. In contrast, eosinophils, which express only low densities of MHC class II and no or only low levels of adhesion molecules (B7, ICAM-1 and LFA3), provided a reduced signal resulting in a diminished IFN-gamma/IL-4 ratio. We conclude that non-classical APC differ in their capacity to restimulate T cell clones, whereby the intensity of MHC class II and adhesion molecules (B7, ICAM-1) expressed seems to determine the efficacy of this presentation.

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Human naive and memory T-helper cells display distinct adhesion properties to ICAM-1, LFA-3 and B7 molecules.

Parra E, Wingren AG, Hedlund G, Sjogren HO, Kalland T, Sansom D, Dohlsten M.

Wallenberg Laboratory, Department of Tumor Immunology, University of Lund, Sweden.

In this paper the contribution of different accessory molecules to the adhesion of resting, naive and memory CD4+ T cells was examined utilizing a panel of CHO cell transfectants as model antigen-presenting cells (APCs). CD4+ T lymphocytes demonstrated strong adhesion to HLA-DR4 transfected CHO cells co-expressing B7, ICAM-1 or LFA-3 molecules, suggesting that all three adhesion pathways is utilized by resting CD4+ cells. Monoclonal antibodies (MoAbs) against the corresponding receptors on T cells, e.g. anti-CD28, anti-LFA-1 beta and anti-CD2, inhibited completely T-cell adhesion to natural ligands expressed on transfected CHO cells. Pretreatment of CD4+ T cells with NKI-L16 MoAb, which interact with an activation epitope on LFA-1 alpha chain, enhanced adhesion to ICAM-1 but not B7 or LFA-3-expressing CHO cells. Analysis of T helper-cell subsets revealed that memory T cells bound several fold stronger to ICAM-1 expressing transfectants compared to the CD4+ 45RA+ naive T cells, whereas adhesion to B7, LFA-3- and B7/LFA-3-expressing CHO cells was similar in both T-cell subsets. The kinetics of adhesion of naive and memory CD4+ T cells to ICAM-1 was rapid and similar in both subsets. The NKI-L16 MoAb multiplied several times ICAM-1-dependent adhesion in naive compared to memory cells, which enabled the naive cells to reach a similar adhesion level as memory cells. The results suggest that resting naive CD4+ T cells utilize preferentially the CD2/LFA-3 or CD28/B7 adhesion pathways upon adhesion to APCs, while memory CD4+ T cells utilize the CD2/LFA-3, CD28/B7 and LFA-1/ICAM-1 adhesion pathways. The NKI-L16 MoAb-induced upregulation of adhesion involves an increased affinity of LFA-1 for its ligand and not a change in the number of LFA-1 molecules. This is compatible with a view that naive cells express a large number of inactive LFA-1 molecules, whereas memory cells express preferentially activated LFA-1 molecules. The inherent low number of active LFA-1 molecules on naive CD4+ T cells may be important in keeping these cells in a resting state.

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A co-stimulatory role for CD28 in the activation of CD4+ T lymphocytes by staphylococcal enterotoxin B.

Goldbach-Mansky R, King PD, Taylor AP, Dupont B.

Laboratory of Human Immunogenetics, Sloan-Kettering Institute for Cancer Research, New York, NY 10021.

In this study we investigated the differential effect of the co-stimulatory receptor ligand molecules CD2/LFA-3, LFA-1/ICAM-1, and CD28/B7 on microbial superantigen mediated activation of CD4+ T cells. Highly purified CD4+ T cells, depleted of antigen presenting cells (APCs), do not proliferate in response to the superantigen, staphylococcal enterotoxin B (SEB). However, CD4+ T cells do respond to SEB in the presence of the LFA-3, ICAM-1, and B7 positive erythroleukemic cell line K562, murine L cells, human B7 transfected L cells or CD28 mAb. The K562 plus SEB induced response can be inhibited by combinations of mAbs to CD2 and LFA-1, and to LFA-3, ICAM-1, and B7. Addition of CD28 mAb to the CD2 and LFA-1 inhibited cultures could restore the response. Furthermore, soluble CD28 mAb alone is able to synergize with SEB to induce a proliferative CD4+ T cell response. CD4+ T cells depleted of APCs could also be activated by a pool of four mAbs directed to the V beta 5, V beta 6, V beta 8, and V beta 12 region of the TCR when a co-stimulatory signal was provided by the CD28 mAb, while the V beta mAbs alone or in combination are unable to activate CD4+ T cells in the absence of APCs. In contrast, addition of soluble mAbs to CD2 and LFA-1 molecules failed to co-stimulate SEB activated CD4+ T lymphocytes. The kinetics of the different modes of activation are distinct. SEB induced proliferation is most efficient in the presence of autologous APCs with maximal proliferation at a log4 lower SEB concentration than when CD28 mAbs were used. SEB plus K562 activation peaks on day 7, while SEB plus CD28 mAb induced proliferative responses do not peak until day 9. Thus, superantigen mediated activation of CD4+ T cells requires co-stimulatory signals, among which CD28 has distinct and unique effects.

PMID: 1363054 [PubMed - indexed for MEDLINE]

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Erratum in:

- J Clin Invest 1993 Apr;91(4):1853

The B7/BB1 antigen provides one of several costimulatory signals for the activation of CD4+ T lymphocytes by human blood dendritic cells in vitro.

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Young JW, Koulova L, Soergel SA, Clark EA, Steinman RM, Dupont B.

Laboratory of Cellular Physiology and Immunology, Rockefeller University, New York 10021.

T cells respond to peptide antigen in association with MHC products on antigen-presenting cells (APCs). A number of accessory or costimulatory molecules have been identified that also contribute to T cell activation. Several of the known accessory molecules are expressed by freshly isolated dendritic cells, a distinctive leukocyte that is the most potent APC for the initiation of primary T cell responses. These include ICAM-1 (CD54), LFA-3 (CD58), and class I and II MHC products. Dendritic cells also constitutively express the accessory ligand for CD28, B7/BB1, which has not been previously identified on circulating leukocytes freshly isolated from peripheral blood. Dendritic cell expression of both B7/BB1 and ICAM-1 (CD54) increases after binding to allogeneic T cells. Individual mAbs against several of the respective accessory T cell receptors, e.g., anti-CD2, anti-CD4, anti-CD11a, and anti-CD28, inhibit T cell proliferation in the dendritic cell-stimulated allogeneic mixed leukocyte reaction (MLR) by 40-70%. Combinations of these mAbs are synergistic in achieving near total inhibition. Other T cell-reactive mAbs, e.g., anti-CD5 and anti-CD45, are not inhibitory. Lymphokine secretion and blast transformation are similarly reduced when active accessory ligand-receptor interactions are blocked in the dendritic cell-stimulated allogeneic MLR. Dendritic cells are unusual in their comparably higher expression of accessory ligands, among which B7/BB1 can now be included. These are pertinent to the efficiency with which dendritic cells in small numbers elicit strong primary T cell proliferative and effector responses.

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Differential costimulatory effects of adhesion molecules B7, ICAM-1, LFA-3, and VCAM-1 on resting and antigen-primed CD4+ T lymphocytes.

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Damle NK, Klussman K, Linsley PS, Aruffo A.

Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121.

Optimal proliferation of T cells although initiated via ligation of the CD3/TCR complex requires additional stimulation resulting from adhesive interactions between costimulatory receptors (R) on T cells and their counter-R on APC. At least four distinct adhesion molecules (counter-R) present on APC, B7, ICAM-1 (CD54), LFA-3 (CD58), and VCAM-1 have been individually shown to costimulate T cell activation. Because some of these molecules may be expressed simultaneously on APC, it has been difficult to examine relative contributions of individual counter-R during the induction of T cell proliferation. We have produced soluble IgC gamma 1 fusion chimeras (receptor globulins or Rg) of B7, ICAM-1, LFA-3, and VCAM-1 and compared their relative abilities to costimulate proliferation of resting or Ag-primed CD4+ T cells. When co-immobilized with mAb directed at TCR alpha beta or CD3 but not CD2 or CD28, each Rg induced proliferation of both resting and Ag-primed CD4+ cells. In contrast, similarly co-immobilized CD7 Rg or ELAM-1 Rg were ineffective. Resting CD4+ T cells produced more IL-2, expressed significantly higher levels of IL-2R alpha, and proliferated more efficiently when costimulated with either ICAM-1 Rg or VCAM-1 Rg than with B7 Rg or LFA-3 Rg. CD4+ CD45RO+ memory T cells proliferated more vigorously in response to the costimulation by each of the four Rg than CD4+ CD45RA+ naive T cells. In contrast with the behavior of resting CD4+ T cells, proliferation of Ag-preactivated CD4+ T cells was most efficient when costimulated by B7 Rg. The costimulatory effect of LFA-3 Rg on Ag-primed CD4+ T cells was weaker than that of B7 Rg but was significantly greater than that of either ICAM-1 Rg or VCAM-1 Rg. These results suggest that resting and Ag-primed CD4+ T cells preferentially respond by proliferation to different costimulatory counter-R. ICAM-1 and VCAM-1 may be involved in the initiation of proliferation of Ag-responsive T cells, and B7 and LFA-3 may facilitate sustained proliferation of Ag-primed T cells. The cumulative costimulation by the above counter-R may facilitate optimal expression of various regulatory and effector functions of T cells.

PMID: 1372018 [PubMed - indexed for MEDLINE]